

## **I. GENERAL INFORMATION**

### **A. File Number**

NADA 039-402

### **B. Sponsor**

Pharmacia & Upjohn Company  
Animal Health Division  
7000 Portage Road  
Kalamazoo, MI 49001

### **C. Trade Name**

MGA® 100/200 Premix, MGA® 500 Liquid Premix

### **D. Generic Name**

melengestrol acetate

### **E. Marketing Status**

Over the Counter (OTC)

### **F. Effect of Supplement**

This supplement provides for the use of melengestrol acetate (MGA) in heifers intended for breeding for suppression of estrus (heat).

## **II. INDICATIONS FOR USE**

Heifers fed in confinement for slaughter: For increased rate of weight gain, improved feed efficiency and suppression of estrus (heat). Heifers intended for breeding: For suppression of estrus (heat).

## **III. DOSAGE**

**A. DOSAGE FORM:** Oral (Feed)

**B. ROUTE OF ADMINISTRATION:** Oral via the feed.

### **C. RECOMMENDED DOSAGES:**

Heifers fed in confinement for slaughter: 0.25 to 0.5 mg MGA per head per day

Heifers intended for breeding: 0.5 mg MGA per head per day

#### IV. EFFECTIVENESS

Effectiveness is established by the data in the parent application. Therefore, no further studies were required.

#### V. ANIMAL SAFETY

The supplemental new animal drug application contains data from adequate and well-controlled investigations demonstrating the safety of MGA for the indications for use and dosage as given in Sections 2 and 3.

##### Pivotal Studies

#### A. Study I: An Oral Reproductive Safety Study in Prepuberal British Beef Heifers Intended as Breeding Animals Dosed for Two 24-Day Periods

1. Type of Study: Oral Reproductive Safety
2. Investigators:

J.R.Chenault, PhD, Study Director  
C.W.Kasson, MS  
R.K.Frank, DVM, PhD  
The Upjohn Company  
Kalamazoo, MI 49001

3. General design of the study:
  - a. *Purpose:* To determine reproductive safety following oral administration of MGA at doses of 0, 0.5 and 1.5 mg/head/day (0, 1X and 3X the maximum approved use level of 0.5 mg/head/day) to heifers while they were prepuberal and again after they had attained puberty.
  - b. *Test animals:* British beef breeds (Angus purebreds and crossbreeds). Four replicates of 11 heifers per dose group; 44 per dose; 3 doses; 132 heifers total. Heifers were prepuberal, 7 to 9 months of age (estimated), at the start of the study and weighed 203 to 309.5 kg.
  - c. *Dose form:* MGA® 200 Premix (finished product; 200 mg MGA/lb) was mixed at two concentrations (0.25 and 0.75 mg MGA/lb) into a feed supplement.
  - d. *Doses used:* 0, 0.5 and 1.5 mg MGA/head/day
  - e. *Route of Administration:* Oral, 2 lb/head/day of the appropriate formulation were fed in feed bunks daily. These diets were completely consumed, each day, before corn silage was offered.
  - f. *Test duration:*
    - (1) Dosing periods: The control diet or the diets containing MGA were fed (2 lb/head/day) daily during two 24-day periods, the first starting on study day 1 while the heifers were prepuberal and the second starting on study day 110 after 80% of the control heifers had been detected in estrus.
    - (2) Response period: The heifers were bred by artificial insemination starting on study day 145, 12 days after the final MGA feeding in the second treatment period; semen from a single collection of one bull was used. All

heifers becoming pregnant during a 74-day breeding period (study days 145-218), which ended 108 days after the start of the second MGA treatment period, were allowed to calve and observations were taken of both dam and calf until 30 days postpartum. Duration of the study was 547 days (78 weeks).

g. Response variables: Responses were categorized into three groups: estrus and reproductive variables [presented in 4.a.], calving and postpartum variables [presented in 4.b.] and body weights [presented in 4.c.].

4. Results:

a. Estrus and reproductive variables: Least squares means by dose group for estrus and reproductive variables are presented in Table 1. The interval from the last day of the first MGA feeding period to first estrus (Days to 1st Estrus) was shorter compared to controls in the 0.5 mg MGA/head/day dose group (31 days vs 56 days for controls,  $P=0.01$ ) but not in the 1.5 mg MGA/head/day dose group (46 days vs 56 days for controls,  $P=0.21$ ).

No differences were detected between either the 0.5 or the 1.5 mg MGA/head/day dose groups and the control group for First Service Conception Rate or Services/Conception whether compared on the basis of All Heifers or Pregnant Heifers (Table 1). Treatment differences were detected between the 0.5 and 0.0 mg MGA/head/day groups for Pregnancy Rate (80% vs 93% for controls,  $P=0.08$ ) and Calving Rate (78% vs 93% for controls,  $P=0.05$ ). No statistically significant ( $P>0.10$ ) differences were detected between the 1.5 and 0.0 mg MGA/head/day dose groups for any of the reproductive variables analyzed.

One set of twin calves was born to a heifer in the 0.0 mg MGA/head/day dose group. Only one abortion was detected among the 113 heifers confirmed pregnant at the end of the breeding period. This heifer was in the 1.5 mg MGA/head/day dose group.

b. Calving and postpartum observations: Least squares means by dose group for calving and postpartum observations are presented in Table 2. Tabular data for calving and postpartum observations, dystocia scores and heifer body condition scores at parturition and 30 days postpartum are presented in Table 3.

No differences were detected between either the 0.5 or the 1.5 mg MGA/head/day dose groups and the control group for abortion rate, duration of parturition, percent with retained placentas, calf weights at 30 days of age, heifer body weight at either parturition or 30 days post partum (Table 2). Differences ( $P=0.07$ ) were detected between the 0.0 and 0.5 mg MGA/head/day dose groups in calf birth weight. No statistically significant differences ( $P>0.10$ ) were detected between the 0.0 and the 1.5 mg MGA/head/day dose groups for any of the calving and postpartum observations. No differences between MGA dose groups and controls are apparent in the data presented in Table 3.

c. Heifer Body Weights: Least squares means for heifer body weights by dose group are presented in Table 4. No statistically significant differences

( $P > 0.10$ ) were detected between the control and either the 0.5 or the 1.5 mg MGA/head/day dose groups for any of the body weight measurements.

**Table 1. Summary of Estrus and Reproductive Response Variables**

Variable	LSMean (P-Value) <sup>1</sup> Dose (mg/head/day)			LSD <sup>2</sup>
	0	0.5	1.5	
<b>Number of Heifers</b> N <sup>3</sup>	44	44	44	
<b>Days to 1<sup>st</sup> Estrus</b> <sup>4</sup>	56	31 (.01)	46 (.21)	13
<b>1<sup>st</sup> Service Conception Rate</b> %	53	57 (.72)	48 (.68)	
<b>Number of Services per Conception (all heifers)</b>	1.9	2.4 (.25)	2.2 (.53)	0.8
<b>Number of Services per Conception (pregnant heifers)</b>	1.6	1.4 (.42)	1.6 (.90)	0.3
<b>Pregnancy Rate</b> %	93	80 (.08)	86 (.32)	
<b>Calving Rate</b> %	93	78 <sup>5</sup> (.05)	84 <sup>6</sup> (.24)	

<sup>1</sup>Least squares means (LSMean). Percent data were transformed to degrees (arcsine transformation) prior to analyses. LSMeans for these data were transformed back to percent for ease of interpretation. P-Values are probabilities of difference from the 0 mg MGA/head/day dose group. P-Values for percent data are from analyses of transformed data.

<sup>2</sup>Least Significant Differences (LSD) are presented only for data that were not transformed prior to statistical analyses.

<sup>3</sup>N = number of animals contributing to the data set.

<sup>4</sup>Days to 1st Estrus = The interval from the last day of the first MGA feeding period to first estrus.

<sup>5</sup>One heifer died after confirmation of pregnancy.

<sup>6</sup>One heifer aborted.

**Table 2. Summary of Calving and Postpartum Observations**

Variable		LSMean (P-Value) <sup>1</sup> Dose (mg/head/day)			LSD <sup>2</sup>
		0	0.5	1.5	
<b>Abortion Rate</b> <sup>3</sup>	<b>N</b> <sup>4</sup>	0/41	0/34	1/38	
	<b>%</b>	0	0 (.5)	3 (.31)	
<b>Parturition Duration</b>	<b>N</b>	27	13	21	1.0
	<b>hr</b>	2.2	2.1 (.88)	1.8 (.54)	
<b>Retained Placentas</b>	<b>N</b>	3/41	1/34	5/37	
	<b>%</b>	7	3 (.56)	14 (.32)	
<b>Calf Birth Weight</b>	<b>N</b>	41	33	34	3
	<b>kg</b>	33	30 (.07)	33 (.94)	
<b>Calf Weight at 30 Days</b>	<b>N</b>	38	30	30	
	<b>kg</b>	50	48 (.46)	51 (.70)	
<b>Heifer Parturition<sup>6</sup> Weight</b>	<b>N</b>	39	33	35	13.1
	<b>kg</b>	413.6	417.6 (.60)	416.2 (.73)	
<b>Heifer Weight 30 Days<sup>7</sup> Postpartum</b>	<b>N</b>	37	31	30	16.3
	<b>kg</b>	434.0	431.3 (.77)	430.9 (.74)	

<sup>1</sup> Least squares means (LSMean). Percent data were transformed to degrees (arcsine transformation) prior to analyses. LSMeans for these data have been transformed back to percent for ease of interpretation. P-Values are probabilities of difference from the 0 mg MGA/head/day dose group. P-Values for percent data are from analyses of transformed data.

<sup>2</sup> Least Significant Differences (LSD) are presented for the non-transformed data, but are not presented for the transformed data.

<sup>3</sup> Abortion rate = number of abortions/number of pregnant heifers. Abortions were defined as parturitions occurring prior to 250 days gestation or undetected losses following a confirmed pregnancy. Homogeneity of treatment variance was rejected and a weighted analysis was used.

<sup>4</sup> N = either (number of animals positive for the variable)/(number of animals eligible for comparison) or the number of animals eligible for comparison. Shown as totals for each dose. Calculated percent from these numbers may not be the same as LSMeans which are determined on a replicate basis.

<sup>5</sup> No statistical comparison with controls made since each had zero abortions.

<sup>6</sup> Weights were taken 0 to 3 days after birth or parturition.

<sup>7</sup> Weights were taken 30 (±2) days after birth or parturition.

**Table 3. Calving and Postpartum Tabular Data**

Variable	Score	Number With Each Score MGA Dose mg/head/day		
		0.0	0.5	1.5
<b>Dystocia Score<sup>1</sup></b>	<b>1</b>	32	31	32
	<b>2</b>	1	0	0
	<b>3</b>	8	3	5
<b>Calf Birth Condition</b>	<b>good</b>	40	33	34
	<b>not good</b>	1	0	0
	<b>dead</b>	1	1	3
<b>BCS<sup>2</sup> at Parturition<sup>3</sup></b>	<b>4</b>	2	1	1
	<b>5</b>	6	5	7
	<b>6</b>	14	10	9
	<b>7</b>	16	16	16
	<b>8</b>	1	1	2
<b>BCS 30 Days<sup>4</sup> Postpartum</b>	<b>4</b>	0	0	0
	<b>5</b>	0	2	1
	<b>6</b>	8	8	9
	<b>7</b>	27	13	16
	<b>8</b>	2	8	4

<sup>1</sup> Dystocia scores were: 1 = Unobserved or unassisted parturition, 2 = One person assist (easy pull) and 3 = Mechanical extraction (hard pull).

<sup>2</sup> BCS = body condition score (1=thinnest, 10=fattest).

<sup>3</sup> Observations made 0 to 3 days postpartum.

<sup>4</sup> Observations taken 30 ( $\pm$ 2) days postpartum.

**Table 4: Summary of Heifer Body Weights**

Variable <sup>2</sup>		LSMean (P-Value) <sup>1</sup> Dose (mg/head/day)			LSD <sup>3</sup>
		0	0.5	1.5	
<b>Weight 1</b>	<b>N<sup>4</sup></b>	44	44	44	4.0
	<b>kg</b>	243.8	244.4 (.76)	243.9 (.97)	
<b>Weight 2</b>	<b>N</b>	44	44	44	
	<b>kg<sup>5</sup></b>	295.8	294.7 (.46)	293.8 (.23)	
<b>Weight 3</b>	<b>N</b>	44	44	44	5.5
	<b>kg</b>	328.5	327.8 (.82)	328.7 (.95)	
<b>Weight 4</b>	<b>N</b>	44	44	44	
	<b>kg<sup>5</sup></b>	398.2	397.1 (.81)	397.8 (.94)	

<sup>1</sup> Least squares means (LSMean). P-Values are probabilities of difference from the 0 mg MGA/head/day dose group.

<sup>2</sup> Weights were recorded on study days 1, 83, 110 and 193 which correspond to the first day of the first MGA feeding period (08 December 1989), 59 days after the first MGA feeding period (28 February 1990), first day of the second MGA feeding period (27 March 1990) and 60 days after the second MGA feeding period (18 June 1990), respectively. These weights correspond, respectively, to heifer weights 1, 2, 3 and 4.

<sup>3</sup> Least Significant Differences (LSD) are presented for the non-weighted analyses, but are not presented for the weighted analyses (see footnote 5).

<sup>4</sup> N = number of animals contributing to the observation.

<sup>5</sup> Homogeneity of treatment variance was rejected and weighted analysis were used. No LSD was calculated because of the weighted analysis.

**B. Study II: An Oral Reproductive Safety Study in Estrous Cycling British Beef Heifers Intended as Breeding Animals Dosed for 24 Consecutive Days**

1. Type of Study: Oral Reproductive Safety
2. Investigators:

J.R.Chenault, PhD, Study Director  
C.W.Kasson, MS  
R.K.Frank, DVM, PhD  
The Upjohn Company  
Kalamazoo, MI 49001

3. General design of the study:
  - a. *Purpose*: to determine reproductive safety following oral administration of MGA at doses of 0, 0.5 and 1.5 mg/head/day (0, 1X and 3X the maximum approved use level of 0.5 mg/head/day) to estrous cycling heifers.
  - b. *Test animals*: British beef breeds (Hereford, Angus and Hereford x Angus Crossbred). Four replicates of 10 heifers per dose group; 40 per dose; 3 doses; 120 heifers total. The heifers were 12 to 14 months of age, weighed 325.0 to 453.0 kg and were all estrous cycling at dose initiation.
  - c. *Dose form*: MGA 200 Premix (finished product; 200 mg MGA/lb) was mixed at two concentrations (0.25 and 0.75 mg MGA/lb) into a feed supplement.
  - d. *Doses used*: 0, 0.5 and 1.5 mg MGA/head/day
  - e. *Route of Administration*: Oral, 2 lb/head/day of the appropriate formulation were fed in feed bunks daily. These diets were completely consumed, each day, before corn silage was offered.
  - f. *Test duration*:

(1) Dosing period: The control diet or the diets containing MGA were fed (2 lb/head/day) daily during a 24-day period (study days 1 through 24).

(2) Response period: The heifers were bred by artificial insemination starting on study day 36, 12 days after the final MGA feeding; semen from a single collection of one bull was used. All heifers becoming pregnant during a 73-day breeding period, which ended on study day 108, were allowed to calve and observations were taken of both dam and calf until 30 days postpartum. Duration of the study was 460 days (66 weeks).

- g. *Response variables*: Responses were categorized into three groups: reproductive variables [presented in 4.a.], calving and postpartum variables [presented in 4.b.] and body weights [presented in 4.c.].
4. Results:
  - a. *Reproductive variables*: Least squares means by dosage group for reproductive variables are presented in Table 5. No differences were detected

between the controls and either the 0.5 or 1.5 mg MGA/head/day dose groups in first service conception rate. Compared to controls, the 0.5 mg MGA/head/day dose group heifers required fewer services/conception (all heifers; 1.8 services vs 2.4 services for controls,  $P=0.03$ ), had an improved pregnancy rate (90% vs 65% for controls,  $P=0.04$ ) and had an increased calving rate (90% vs 63% for controls,  $P=0.03$ ). A statistically significant increase in services/conception compared to controls was observed for both the 0.5 mg MGA/head/day heifers (1.5 vs 1.2 in controls,  $P=0.08$ , Table 5) and the 1.5 mg MGA/head/day heifers (1.6 vs 1.2 for controls,  $P=0.04$ , Table 5) when comparing only the heifers that became pregnant.

b. Calving and postpartum observations: Least squares means by dosage group for calving and postpartum variables are presented in Table 6. No statistically significant differences ( $P=0.11-0.78$ ) were detected between the 0.0 mg MGA/head/day dose group and either the 0.5 or the 1.5 mg/head/day MGA dose groups for any of the calving or postpartum observations. Tabular data for calving and postpartum observations of dystocia and heifer body condition scores are presented in Table 7. No differences between MGA dose groups is apparent in this tabular data. Mean body condition score for heifers in the control, 0.5 and 1.5 mg MGA/head/day dose groups was 6.4, 6.5 and 6.5 at parturition and was 6.5, 6.6 and 6.8 at 30 days postpartum, respectively.

c. Heifer body weights: Least squares means for body weights by treatment group are presented in Table 8. No statistically significant differences ( $P=0.60-0.99$ ) were detected between the control and either the 0.5 or the 1.5 mg MGA/head/day dose groups for body weight measurements recorded on the first day of MGA feeding and 63 days after the last MGA feeding.

**Table 5. Summary of Reproductive Variables**

Variable		LSMean (P-Value) <sup>1</sup> MGA Dose (mg/head/day)			LSD <sup>2</sup>
		0	1.5	1.5	
<b>Number of Heifers</b>	<b>N<sup>3</sup></b>	40	40	40	
<b>1<sup>st</sup> Service Conception Rate</b>	<b>%</b>	53	60 (.31)	48 (.53)	
<b>Services/Conception (all heifers)</b>	<b>No.<sup>4</sup></b>	2.4	1.8 (.03)	2.1 (.23)	0.5
<b>Services/Conception (pregnant heifers)</b>	<b>No.</b>	1.2	1.5 (.08)	1.6 (.04)	0.2
<b>Pregnancy Rate</b>	<b>%</b>	65	90 (.04)	78 (.28)	
<b>Calving Rate</b>	<b>%</b>	63	90 (.03)	78 (.21)	

<sup>1</sup> Least squares means (LSMean). Percent data were transformed to degrees (arcsine transformation) prior to analyses. LSMeans for these data have been transformed back to percent for ease of interpretation. P-Values are probabilities of difference from the 0 mg MGA/head/day dose group. P-Values for percent data are from analyses of transformed data.

<sup>2</sup> Least Significant Differences (LSD) are presented only for data that were not transformed prior to statistical analyses.

<sup>3</sup> N = number of animals contributing to data sets.

<sup>4</sup> No. = number of services/conception.



**Table 6. Summary of Calving and Postpartum Observations**

Variable		LSMean (P-Value) <sup>1</sup> MGA Dose (mg/head/day)			LSD <sup>2</sup>
		0	0.5	1.5	
<b>Abortion Rate</b> <sup>3</sup>	<b>N</b> <sup>4</sup>	1/26	0/36	0/31	
	<b>%</b>	4	0 (.11)	0 (.16)	
<b>Parturition Duration</b>	<b>N</b>	7	13	12	1.2
	<b>hr</b>	2.2	2.7 (.42)	1.7 (.48)	
<b>Retained Placenta</b>	<b>N</b>	2/25	3/36	4/31	
	<b>%</b>	7	8 (.76)	11 (.64)	
<b>Calf Birth<sup>5</sup> Weight</b>	<b>N</b>	25	35	30	2.0
	<b>kg</b>	31.3	31.8 (.68)	31.5 (.78)	
<b>Calf Weight at 30 Days<sup>6</sup></b>	<b>N</b>	25	34	29	3.9
	<b>kg</b>	54.0	55.8 (.43)	53.3 (.72)	
<b>Heifer Parturition<sup>5</sup> Weight</b>	<b>N</b>	25	36	31	11.4
	<b>kg</b>	451.0	445.8 (.43)	447.1 (.54)	
<b>Heifer Weight 30 Days<sup>6</sup> Postpartum</b>	<b>N</b>	24	34	29	13.8
	<b>kg</b>	460.9	450.0 (.18)	452.3 (.28)	

<sup>1</sup> Least squares means (LSMean). Percent data were transformed to degrees (arcsine transformation) prior to analyses. LSMeans for these data have been transformed back to percent for ease of interpretation. P-Values are probabilities of difference from the 0 mg MGA/head/day dose group. P-Values for percent data are from analyses of transformed data.

<sup>2</sup> Least Significant Differences (LSD) are presented for the non-transformed data, but are not presented for the transformed data.

<sup>3</sup> Abortion rate = number of abortions/number of pregnant heifers. Abortions were defined as parturitions occurring prior to 250 days gestation or undetected losses following a confirmed pregnancy.

<sup>4</sup> N = either (number of animals positive for the variable)/(number of animals eligible for comparison) or number of animals eligible for comparison. Shown as totals for each dose. Calculated percent from these numbers may not be the same as LSMeans which are determined on a replicate basis.

<sup>5</sup> Weights were taken 0 to 3 days after birth or parturition.

<sup>6</sup> Weights were taken 30 (±2) days after birth or parturition. The calf from one heifer in the 0 mg MGA/head/day dose group was on a foster dam not in this study and the heifer was excluded.

**Table 7. Calving and Postpartum Tabular Data**

Variable	Score	Number With Each Score MGA Dose mg/head/day		
		0.0	0.5	1.5
<b>Dystocia Score<sup>1</sup></b>	<b>1</b>	24	33	30
	<b>2</b>	0	1	0
	<b>3</b>	1	2	1
<b>Calf Birth Condition<sup>2</sup></b>	<b>good</b>	24	32	28
	<b>not good</b>	1	3	2
	<b>dead</b>	1	1	1
<b>BCS<sup>3</sup> at Parturition<sup>4</sup></b>	<b>4</b>	0	0	2
	<b>5</b>	3	6	3
	<b>6</b>	10	11	7
	<b>7</b>	11	14	16
	<b>8</b>	1	5	3
<b>BCS 30 Days<sup>5</sup> Postpartum</b>	<b>4</b>	0	0	1
	<b>5</b>	3	4	2
	<b>6</b>	9	12	6
	<b>7</b>	9	12	14
	<b>8</b>	3	6	6

<sup>1</sup> Dystocia scores were: 1 = Unobserved or unassisted parturition, 2 = One person assist (easy pull) and 3 = Mechanical extraction (hard pull).

<sup>2</sup> The dead calf in the 0 mg MGA/head/day dose group was the calf aborted.

<sup>3</sup> BCS = body condition score (1=thinnest, 10=fattest).

<sup>4</sup> Observations made 0 to 3 days postpartum.

<sup>5</sup> Observations taken 30 (±2) days postpartum. One calf in the 0 mg MGA/head/day dose group was on a foster dam.

**Table 8. Summary of Heifer Body Weight Data**

Variable <sup>2</sup>		LSMean (P-Value) <sup>1</sup> Dose (mg/head/day)			LSD <sup>3</sup>
		0	0.5	1.5	
<b>Weight 1</b>	<b>N<sup>4</sup></b>	40	40	40	4.7
	<b>kg</b>	380.1	380.0 (.96)	380.2 (.99)	
<b>Weight 2</b>	<b>N</b>	40	39 <sup>5</sup>	40	6.4
	<b>kg</b>	429.6	429.3 (.94)	427.7 (.60)	

<sup>1</sup> Least squares means (LSMean). P-Values are probabilities of difference from the 0 mg MGA/head/day dose group.

<sup>2</sup> Heifers were weighed on study days 1 (Weight 1) and 87 (Weight 2) which correspond to the first day of the MGA feeding period and 63 days after the last day of the MGA feeding period, respectively.

<sup>3</sup> Least Significant Differences (LSD).

<sup>4</sup> N = number of animals contributing to the observation.

<sup>5</sup> One heifer was missed at this weighing.

## C. Conclusions

1. For Study I (MGA initially fed to prepubertal heifers for a 24-day period, and repeated for an additional 24-day period after the heifers had reached puberty), negative effects were observed for pregnancy rate, calving rate,

and calf birth rate at the 1X level (0.5 mg/head/day), but not at the 3X level (1.5 mg/head/day). Pregnancy rate and calving rate were seen to decrease by 13- 15% for the 1X group compared to controls. However, no differences were seen between the 3X group and controls. Likewise, calf birth weight was seen to decrease for the 1X group compared to controls (33 kg for controls vs. 30 kg for 1X group), but no differences were observed between the 3X group and controls (33 kg for controls vs. 33 kg for 1X group). No other negative effects on reproduction were seen for the remaining reproductive variables studied.

2. For Study II ( MGA fed to cycling heifers for one 24- day period), no negative effects were observed on reproduction for any of the variables studied (except for an increase in services/conception in heifers that became pregnant). In contrast to Study I, positive effects were observed for feeding MGA on services/conception (when all heifers are compared), pregnancy rate, and calving rate.
3. The positive effects observed for MGA in Study II along with the fact that no differences were seen between 3X and controls for Study I provide substantial evidence that MGA has little or no negative effect on reproduction when fed to cycling heifers for up to 24 days. Based on this, the negative effects of MGA observed at the 1X level in Study I on pregnancy rate, calving rate, and birth weight are considered not real. Accordingly, it is concluded that feeding MGA at 0.5 mg/head/day to heifers for up to 24 days does not have a negative effect on reproduction.

## **VI. HUMAN FOOD SAFETY**

Human safety is established by the data in the parent application. Therefore, no further studies were required.

## **VII. AGENCY CONCLUSIONS**

Adequate data demonstrates the safe and effective use of MGA in heifers intended for breeding for suppression of estrus (heat).

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change providing for the use of MGA in heifers intended for breeding for suppression of estrus (heat). The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the change in the labeling (providing for the use of MGA in heifers intended for breeding for suppression of estrus (heat)) for which the supplemental application was approved.

**VIII. LABELING (ATTACHED)**

Four (4) pages of labeling are attached as follows:

Bag Label (front) for MGA 100 Premix (Type A medicated article)  
Bag Label (Back) for MGA 100 Premix (Type A medicated article)  
Bag Label (front) for MGA 200 Premix (Type A medicated article)  
Bag Label (Back) for MGA 200 Premix (Type A medicated article)  
Blue Bird label for dry Type B supplement containing MGA  
Pail Label (front) for MGA 500 Liquid Premix (Type A medicated article)  
Pail Label (back) for MGA 500 Liquid Premix (Type A medicated article)  
Blue Bird label for liquid Type B supplement containing MGA

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration  
Freedom of Information Staff (HFI-35)  
5600 Fishers Lane  
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.